REMARKS

Reconsideration and allowance of the present application are respectfully requested. Claims 1-22, 24-40, 42-71 and 73-80 remain pending in the application. By the foregoing amendment claims 1, 2, 8, 9, 11, 12, 18, 19, 22, 24, 26-28, 30, 31, 37, 38, 40, 42-44, 47, 48, 54-56, 60, 61, 67-71, 73, 75 and 76 are amended; claims 23, 41 and 72 are canceled; and claims 78-80 are added.

The Information Disclosure Statement filed October 21, 2005 has not yet been acknowledged. The Examiner is respectfully requested to acknowledge consideration of the cited references by return of an initialed copy of Form PTO 1449, attached, or if unable to do so, the Examiner is respectfully requested to particularly point out the deficiencies requiring correction or resubmission by the Applicants.

Applicants note with appreciation the Examiner's indication on page 7 of the Office Action that claims 23-28, 41-46 and 72-77 contain allowable subject matter. In response, certain of the allowable subject matter have been clarified and incorporated in the respective independent claims.

Applicants wish to thank Examiner Wallenhorst for the brief telephone discussion on March 20, 2006 with an Applicants' representative, Mr. Richard J. Kim. The informal discussion briefly covered the allowable subject matters as indicated on page 7 of the Office Action. Based on the discussed allowable subject matters, Applicants provide the amended claims and the remarks that follow.

In numbered paragraph 2, page 2 of the Office Action, claims 2-9, 18-46, 48-58 and 67-77 are rejected under 35 U.S.C § 112, second paragraph, as being indefinite. To address the Examiner's concerns, the relevant claims are amended.

However, with respect to claim 20, Applicants respectfully submit that original claim 20 correctly recites "The method of claim 19, further providing a control batch of said sample, applying no stress factor to said control batch, and detecting the increase in particle agglomeration in said control batch after the passage of said time interval Δt." Withdrawal of the rejection is respectfully requested.

Prior Art Rejections

In numbered paragraph 5, page 3 of the Office Action, independent claims 1 and 47, along with various dependant claims, are rejected under 35 U.S.C §102(b) as being anticipated by Nicoli et al., "Particle size analysis of colloidal suspensions by SPOS compared to DLS:A sensitive indicator of quality and stability," American Laboratory, vol. 33(1), January 2001, pp. 32-39). In numbered paragraph 8, page 5 of the Office Action, independent claim 40, along with various dependant claims, are rejected as being unpatentable over the Nicoli et al. article. In numbered paragraph 9, page 6 of the Office Action, various dependant claims are rejected as being unpatentable over the Nicoli et al. article in view of Friberg et al. "Theory of Emulsions," Pharmaceutical Dosage Forms: Disperse Systems, Lieberman et al. (eds.), Vol. 1, 1988, page 66. These rejections are respectfully traversed.

Applicants' disclosure encompasses applying "stress" systematically to a sample, in the form of one or more small perturbations of the inter-particle repulsive force that influences the present level of stability of a given sample. The resulting accelerated time behavior of the growth in particle agglomeration can then reveal the underlying degree of stability (or lack thereof) of the sample (e.g., page 37, lines 8-20). The sample at the outset typically does not necessarily possess significant particle agglomeration as indicated by an extensive PSD tail of "over-size" particles

(e.g., page 38, lines 1-3). Samples which otherwise appear to be similar and substantially equal with respect to the extent of particle agglomeration (as revealed by their PSD tails) can be distinguished as "more stable" and "less stable" (and to what extent) through the systematic application of appropriate stress factors at appropriate stress levels, which have the effect of increasing the rate of particle agglomeration to a level that is high enough that the resulting changes (i.e., increases) in the number or concentration of larger particle agglomerates can be observed over a relatively short time interval. The resulting new, enhanced rate of particle agglomeration is designed, as taught in the Applicants' disclosure, to be well above the normal, underlying rate, which typically is too small to be measured over a reasonable elapsed time interval.

The novelty of the present application in this regard can be greatly appreciated by the previous comments of Friberg et al. and Breuer as outlined in 2. In the *Description of the Related Art.*, Friberg et al. state:

> *The dilemma for the formulator of an emulsion lies in the fact that the success of a preparation can be judged only after a long time. If shelf-life of one year is needed, it is in principle necessary to wait one year to find out whether a large number of samples still are intact.*

Breuer states:

> *Predicting long-term stability from accelerated laboratory test still remains an elusive goal. In spite of its great commercial importance, only a small amount of fundamental research is being carried out on the problem. One of the reasons for this relatively*

low interest is, no doubt, due to the very long time periods that are required (e.g., 2 years of storage) for validating the results of any new predictive technique.

These two observations from notable experts in emulsion science clearly establish the void that existed up to the time of the present invention. In the present application for example, the behavior of whole milk (unstressed) showed relatively consistent initial or starting PDP concentrations (as shown in Figure 5) does not foretell performance under stress or verify the assignment expiration dates. The behavior of whole milk with pH stress uncovered the fact the significant flaws in expiration date, thus attributing the results to flawed homogenization and handling procedures. Figures 24 and 25 of the present application illustrate the general profiles to be expected under selected circumstances.

The concept of "stability" assessment, as disclosed by the Applicants, includes the concepts of elapsed time (i.e., of the dynamics of particle agglomeration) and degree of immunity to destabilizing influences (e.g., page 37, lines 20-22). Applicants have relied upon the fact that an inter-particle repulsive energy barrier height may be usefully lowered by a given, typically relatively small, amount due to a change in pH or addition of a screening salt or adsorbing electrolyte. The resulting rate of particle agglomeration, typically much higher than the underlying rate before systematic application of stress, is then large enough to be measured over a relatively short time period and used to determine the degree to which the system can be described as "stable", before application of stress.

The stability is quantitatively determined based on determined rates of agglomeration of suspension or dispersion systems by accelerating the

agglomeration process. While two samples may be suspected of differing in "stability", they will typically appear to be similar, if not identical, with respect to their particle size distributions (PSDs), including the extent of their large-particle outlier "tails" associated with particle agglomerates. These two samples will typically not reveal their differences with respect to agglomeration until an excessively long time has elapsed.

Hence the desirability of being able to accelerate the particle agglomeration process to the point where the rate of agglomeration can be measured over a suitable short time interval, including allowing this measurable rate to be further increased by the judicious application of yet stronger levels of an appropriate stress factor. In commercial production of a batch or batches of a particular emulsion system, for example, application of the present invention could allow corrective in-process intervention(s) to save the current batch and/or alter manufacturing processes for production of future batches of superior stability.

Applicants have disclosed applying a level, or series of levels, of a stress factor to the system and making a series of measurements of the PSD tail as a function of elapsed time for each stress level (e.g., page 35, lines 7-18). Subsequently, the results of these stresses can be evaluated by, for example, the percentage of the dispersed phase (PDP) implicated in the PSD tail is measured. From one or more derivatives of the PDP with respect to time and/or stress level, an appropriate figure of merit (FM) of the system can be constructed, from which the underlying stability of the system can be estimated quantitatively.

Applicants have disclosed that the extent of the agglomerated PSD tail, as measured by the PDP, can be used to infer the quality of a sample, independent of

the dynamics (i.e. rate of increase) of the particle agglomerate population, but that stability of the sample can only be separately ascertained by determining the rate of change of the PDP with elapsed time (i.e., for a given applied stress level) or the rate of change of the PDP with increasing stress level (i.e., for a given elapsed time).

Claims 1, 40, 43 and 47 have been amended to clarify and incorporate certain of the allowable claim features. Claim 1 encompasses a method or apparatus for determining the stability of a sample including, among other features, applying a stress factor to said sample to reduce a height of an interparticle potential energy barrier so as to accelerate the rate of particle agglomeration, computing a rate of change, such as a percentage of dispersed phase (PDP) associated with relatively large particles, representing particle agglomerates with elapsed time for a given applied level of stress factor; and detecting an increase in rate of particle agglomeration as a measure of the stability.

Claim 40 recites application of the above method to, among other features, ascertain detection of an increase in rate of agglomeration to calculate a percentage of the dispersed phase (PDP) associated with a tail of large-diameter outlier particles from a measured PSD, and computing a rate of change of said PDP with elapsed time.

Claim 43 encompasses the applied calculation of the measured change, using for example, the percentage of the dispersed phase (PDP) associated with a tail of large-diameter outlier particles from a measured PSD; and computing the increase in said PDP per unit change in applied stress factor for a given value of elapsed time.

Claim 47 encompasses the collective means for computing a rate of change of a percentage of the dispersed phase PDP with elapsed time for a given applied

level of stress factor and for detecting an increase in rate of particle agglomeration as a measure of the stability.

The Nicoli et al. Article

In numbered paragraph 5, page 3 of the Office Action, the Examiner asserts that "Nicoli et al teach of a method and apparatus for measuring the stability of colloidal suspensions (dispersions of solid or liquid particles suspended in a liquid carrier)." This assertion is respectfully traversed.

The applied article teaches how the quality of a colloidal suspension can be assessed using the technique of particle size analysis (and, more particularly, SPOS). The article discloses an example of a clearly defined and well-publicized a "destabilized" fat emulsion system, in which the PSD, including large-particle tail, was seen to evolve toward larger particle sizes over a period of time. In the case of this "poor quality" (from the point of view of stability) sample, the time interval over which significant increases in particle agglomeration occurred, as indicated by the progressive changes in the measured PSD "snapshots" (Fig. 4), was relatively short – i.e., only about 12-24 hours, depending on the emulsion. (Results obtained from similar successive PSD "snapshots" for fat emulsions of differing "quality" (with respect to the relative presence or absence of oversize fat globules) over a similar time scale are discussed in the two articles of Driscoll et al published in Int'l Journal of Pharmaceutics, as cited recently by the Examiner.)

There was no teaching provided in the article that would indicate how a systematic, gentle perturbation of the physical mechanism responsible for providing stability to the fat droplets (i.e., interparticle electrostatic repulsive forces) could be usefully employed, by applying small, calibrated, incremental stress levels to the

system. The example of the artticle showed different "snapshots" of a specific emulsion system known to be unstable. There was no suggestion of measuring an increase in the rate of particle agglomeration that results from a given level of applied stress.

A given system of interest may possess a high enough level of stability to reveal no measurable rate of particle agglomeration over a tolerable length of time – the usual case for typical "good" samples. Alternatively, a sample may possess a low enough level of stability that its underlying rate of particle agglomeration is sufficiently high that it can be reliably determined by making suitable measurements over a relatively short period of time. But in either extreme case, the time scale for accelerating the rate of particle agglomeration in order to make effective measurements thereof, as described by the Applicants, is much shorter than the characteristic time over which the underlying rate of particle agglomeration occurs in the absence of stress application.

In numbered paragraph 5, page 3 of the Office Action, the Examiner asserts that "Nicoli et al teach that the stability of colloidal suspensions can be analyzed by applying a stress factor to the suspension, such as the addition of excessive amounts of electrolyte to the suspension or by thermal or pH shock (i.e. changing the temperature or pH of the suspension)." This assertion is respectfully traversed.

The applied article does not teach a method for analyzing the stability of colloidal suspensions. All that was pointed out in the Nicoli et al article was the known disclosure that subjecting typical colloidal suspensions to significant destabilizing forces associated with "excessive amounts of electrolyte" or "thermal or

pH shock" is often sufficient to produce significant increases in particle agglomerates as well as much higher rates of formation of the same.

The applied article disclosed two examples: CMP slurry and fat emulsion of suspension or emulsion systems for which their underlying stability could be massively degraded through the application of a change of temperature or pH. In the case of CMP slurry, there is also the well-known mechanism of "shear stress". The use of such physical variables is well known to cause a wide variety of suspensions or emulsions to degrade significantly in quality. Such a transition from relatively "good quality" to relatively "poor quality" involves degradation in the "stability" of the system in question. This approach would contradict the criticisms and numerous examples of the reasons for the failures of prior attempts at accelerated stability testing with emulsions involving such overwhelming stress influences as outlined in the Description of the Related Art.

The applied article does not teach or suggest a method for obtaining a quantitatively useful assessment of the level of stability of a given system (e.g., where the underlying rate of particle agglomeration is typically so slow as to reveal no meaningful changes in the PSD, agglomerate particles included, over a practical (short) period of time). The references cited in Applicants' Prior Art section have disclosed that (in the absence of the instant invention) there were no reliable methods in existence for assessing the stability of emulsions and suspensions without simply waiting for excessive lengths of time in order for observable changes in the samples associated with particle agglomeration to manifest themselves. The applied article does not address the systematic application of modest increments in stress to the system in order to probe in a quantitatively meaningful (i.e., predictive)

way its sensitivity, or susceptibility, to such applied stress. The applied article would not have taught or suggested a useful, quantitative assessment of the degree of stability of the system, but rather only a means of characterizing the current state of a specific and "untouched" emulsion system.

The Nicoli et al. article does not describe determining the increase in rate of particle agglomeration in a given sample due to a systematic decrease in barrier height. Isolated "snapshots" of the PSD, relatively widely separated in time, such as those shown in the article for a fat emulsion and a silica CMP slurry, do not teach or suggest determination of a quantitative measure of the stability of the sample with respect to particle agglomeration (e.g., Figs. 4-6).

In numbered paragraph 5, page 4 of the Office Action, the Examiner asserts that "This sensitivity is required to ascertain the quality and stability of a product." This assertion is respectfully traversed. The high sensitivity (i.e., to individual particles) afforded by the SPOS technique is shown in the applied article to enable the determination of only the quality of a product (albeit with high sensitivity to subtle changes therein) – i.e., the relative presence, or lack thereof, of large-particle outliers in the PSD tail. The applied article discloses systems that are relatively "stable" or relatively "unstable", but it clearly fails to teach the method of systematic perturbation of system stability through the judicious application of modest, incremental levels of stress, as encompassed by the present application. The applied article showed that the SPOS technique was one way to evaluate the current state of an emulsion system, and was capable of showing these changes over time in a fixed emulsion system known to be unstable.

The Nicoli et al. article relates to ascertaining individual, isolated "snapshots", separated by relatively long time intervals, of the quality of a sample as indicated by a particle size distribution (PSD) of the latter. The Nicoli et al. article does not determine the stability of samples in a manner as presently claimed.

The Nicoli et al. article describes two concepts. First, the quality of a sample, as represented for example by the extent to which particles in the sample have become agglomerated, can often be ascertained by measuring the particles that populate the large-diameter "tail" of the PSD. Second, this tail can indeed be quantified using the sensitive technique of SPOS. To the extent that a given sample exhibits a PSD tail of agglomerates that is observed to grow over a relatively short period of time, that sample will therefore be identified as being of relatively "poor quality", in the sense that it is relatively "unstable", or possesses a relatively low level of stability. Otherwise, and much more typically, the isolated "snapshots" provided by repeated measurements of the PSD will be substantially similar and therefore useful only in establishing the level of "quality" of the sample, revealing no useful information about the underlying level of "stability" of the system.

The SPOS method disclosed in the Nicoli et al. article does not determine a quantitative stability of the CMP slurry samples. The word "stability" as used in the article connotes quality of characteristics and/or performance of the sample, rather than constancy, or "stability," of the latter over time. As disclosed in the Nicoli et al. article, in the case of the CMP slurry samples, the concentration and size of the outlier particles that define the upper tail of the PSD serve as a quantitative indicator of the quality of the slurry.

Second, known physical mechanisms are responsible for growth in the PSD tail for these slurries. These abnormally large particles are usually aggregates of the smaller primaries, typically produced by mechanical stress or thermal/pH shock of the slurry (e.g., last column of page 34). The article disclosure relates to the quality of the slurry and the fact that it could be significantly degraded by well-known physical mechanisms, and not a means for determining the degree of quantitative stability of the CMP slurry samples. Emulsion systems are widely known to become unstable by changes in the tail of the PSD by varying classifications of stability known as agglomeration or aggregation of the smaller dispersed particles or droplets which will eventually coalesce into very large-diameter flocs or globules. The applied article essentially showed "before and after" snapshots of this process.

The "before" and "after" results shown and discussed in the Nicoli et al article basically show suspensions that contain either relatively small populations of large agglomerates or very large populations, following substantial destabilization. The Nicoli et al. article does not describe levels of stress applied to these systems, and does not describe accelerated stress testing of particle suspensions.

The Nicoli et al. article would not have taught or suggested computing a rate of change (increase) of a percentage of dispersed phase PDP associated with the large-particle PSD tail containing particle agglomerates and detecting an increase in rate of particle agglomeration as a measure of the stability as claimed.

The Friberg et al. reference

In numbered paragraph 8, page 5 of the Office Action, the Examiner asserts "these steps would have been obvious to one of ordinary skill in the art in order to analyze and determine what level of stress factor is required to cause a colloidal

suspension to become unstable, and how long/what level of the stress factor must be applied to the colloidal suspension in order to render it unstable." This assertion is respectfully traversed.

Suspensions and emulsions do not come in two categories, "stable" and "unstable". Rather, all suspensions and emulsions are thermodynamically unstable to one degree or another. All systems undergo particle agglomeration over time. The key distinction that distinguishes one system, or sample, from another concerns the rate at which the mechanism of particle agglomeration occurs. The rate at which agglomeration occurs for a given system is not addressed by the Friberg et al. reference. A "good", relatively stable system, exhibits a relatively slow rate of agglomeration. A "bad", relatively unstable system, exhibits a relatively fast rate of agglomeration. It is only with the benefit of the present application that one of ordinary skill can ascertain quantitatively in an accelerated fashion the relatively low degree of stability of an emulsion.

The Friberg et al. reference was cited in Applicants' Prior Art section which made it clear that there was no known method to determine reliably the stability of a given emulsion or suspension. In addition to the relevant quotes above from Friberg and as noted in the Description of the Related Art, he also states:

> *This problem would be avoided if a reliable method for accelerated testing were found; that is, if a method were available that made it possible to judge the long-term behavior from short-term changes. Unfortunately a general method of this kind is not available. There are methods in use that accelerate the destabilization process for emulsions of specific kinds, and these*

are useful within their realm of application. On the other hand, the important fact that these methods may give completely erroneous results when applied outside their established realm cannot be overemphasized.

In numbered paragraph 9, page 6 of the Office Action, the Examiner asserts "This change with salt concentration results in a loss of stability in the emulsion due to the agglomeration of the particles therein." Notwithstanding the Examiner's assertion, the Friberg et al. reference does not disclose adding salt specifically to ascertain quantitatively in an accelerated fashion the relatively low degree of stability of an emulsion.

In numbered paragraph 9, page 6 of the Office Action, the Examiner asserts "Friberg et al teach that the change from a stable emulsion to an unstable one takes place at a well-defined salt concentration." Notwithstanding the Examiner's assertion, the mechanism described in Friberg et al. reference is a "hammer blow" that effectively destroys the character and characteristics of the starting emulsion or suspension, but does not teach or suggest accelerated agglomeration of particles as claimed. The continuum of "degrees of stability" encompassed by the recited claim features, and exemplified by plots of the PDP results from experiments disclosed in the Applicants' disclosure, would not have been taught or suggested by the "all-or-nothing" mechanism of emulsion "destabilization" of the Friberg et al. reference. Friberg et al. cited above would not be consistent with the Examiner's interpretation. In fact, the Friberg et al comment "*... the change from a stable to an unstable emulsion takes place a well-defined electrolyte concentration*" is so stated on p. 66 of their chapter and the aforementioned Frieberg et al. comments appear near the end

of it at pp. 70-71. So it would not have made sense for Friberg et al. to imply that the principles of the present invention would have been known, and subsequently conclude with outstanding deficiencies in identifying unavailable method(s).

The Friberg et al. reference does not cure the deficiencies of the Nicoli et al. article. The Friberg et al. reference was applied for its disclosure of an application of salt concentration to yield highly agglomerated states, necessarily resulting in virtual destruction of the original emulsion or dispersion system, owing to effective separation of the particle (solid or liquid) and solvent phases. The Friberg et al. document does not relate to the claimed stability of an emulsion or dispersion. Thus, there is no "well-defined salt concentration" that converts a suspension from being "stable" to being "unstable", as proven by the experimental results provided in the Applicants' disclosure. The Friberg et al. document would not have taught or suggested computing a rate of change, such as via a percentage of dispersed phase PDP implicated in the PSD tail and associated with particle agglomerates and detecting an increase in rate of particle agglomeration as a measure of the stability.

Further, the Friberg et al. document does not contemplate a controlled application of relatively small stress levels to emulsion systems having different underlying stability, or rates of particle agglomeration, normally too small to measure over a reasonable time. Accordingly, the Friberg et al. document is not directed to determining the stability of emulsions and other colloidal dispersions as claimed. For at least these reasons, the Friberg et al. document does not cure the deficiencies of the Nicoli et al. article.

In numbered paragraph 9, page 6 of the Office Action, the Examiner asserts:

> Based upon the combination of Nicoli et al and Friberg et al, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to perform the stability testing method taught by Nicoli et al by adding a salt such as sodium chloride to a colloidal suspension as the stress factor since Friberg et al teach that the addition of a salt to an emulsion serves to render the emulsion unstable by reducing the repulsion potential and the barrier height between the particles, similar to the action of changing the pH or adding an electrolyte to the colloidal suspension.

This assertion is respectfully traversed. The Nicoli et al. article would not have taught or suggested a method for determining a measure of the stability of a sample as claimed. The Friberg et al. reference relates to "extreme" destabilization, or virtual destruction, of an emulsion, and cannot be combined with the Nicoli et al. article. Even if combined as suggested by the Examiner, the particle size analysis of colloidal suspensions by SPOS as disclosed in the Nicoli et al. article and the addition of a salt to an emulsion to render the emulsion unstable as disclosed in the Friberg et al. would not have resulted in the claimed method for determining a measure of the stability of a sample based on reducing the stability of a system by modestly accelerating the rate of particle agglomeration.

Conclusion

None of these documents, considered individually or in the combination as relied upon by the Examiner, would have taught or suggested computing a rate of

change of a percentage of dispersed phase PDP and detecting an increase in rate of particle agglomeration as a measure of the stability of a sample.

As such, Applicants' independent claims 1, 40, 43 and 47, along with all claims which depend therefrom, are allowable. All objections and rejections raised in the Office Action having been addressed, it is respectfully submitted that the application is in condition for allowance and a Notice of Allowance is respectfully solicited.

Respectfully submitted,

BUCHANAN INGERSOLL PC

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Attached: Copy of Form PTO 1449

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